IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No.: 08/823,999 Art Unit: 1644

Filed: March 25, 1997 Examiner: Phillip Gambel

For: *MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*

PREVIOUS APPEAL NO: 2003-0074

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

This is a reply to the Examiner's Answer mailed December 9, 2004 in the above identified patent application. A request for Oral Hearing is enclosed along with the appropriate fee for a small entity. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

Appellants have appealed the rejection of claims 1-12 in the Office Action mailed October 30, 2003. A Notice of Appeal was filed on January 30, 2004. An Appeal Brief was filed July 21, 2004. A Substitute Appeal Brief was filed August 10, 2004 in response to the Notification of Non-Compliance with 37 C.F.R. § 1.192(c) mailed on July 27, 2004.

U.S.S.N.: 08/823,999
Filed: March 25, 1997
REPLY TO EXAMINER'S ANSWER

(3) STATUS OF CLAIMS ON APPEAL

There appears to be a major difference in opinion as to what claims are on appeal and what has been searched. It is clear that the examiner's rejections under 35 U.S.C. 112, first and second paragraph, relate to the full scope of claims 1-12, not just some claims or some elected species. It appears that the examiner is addressing this issue on page 4 of the Reply Brief, but differently from the way it has been addressed throughout the long and convoluted history of this application. It is quite clear from the discussion on page 7, however, that the claims have been examined with respect to their full scope in regard to enablement and indefiniteness and written description.

It is believed, and earnestly solicited, that the Board decide all 112 issues with respect to the full scope of the claims. This would greatly expedite review of a case that has been pending for many years and where the examiner has adopted a completely inflexible approach that insures the case will be back on appeal if there is any undecided issue remaining after the decision on this appeal. The time and cost of this prosecution has already been unduly burdensome for the non-profit assignee, and delayed all further clinical development pending a favorable outcome. The assignee does not have the funding to return for a third appeal.

With respect to the prior art rejections, the examiner has cited art that is applicable to multiple species, not just an antibody to Mac 1 (also known as anti CD11b/CD18).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) do claims 1-9, 11 and 12 have written description under 35 U.S.C. § 112, first paragraph;

(2) do claims 1-12 lack enablement under 35 U.S.C. § 112, first paragraph;

(3) are claims 1-12 indefinite under 35 U.S.C. § 112, second paragraph;

(4) are claims 1-6, 8 and 10-12 disclosed under 35 U.S.C. §102(a)(b) (presumably one or the other) by Genetta, et al., Ann. Pharmacol. 30:251-257 (1996) in view of Schwarz, et al., Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999);

(5) are claims 1-6, 8 and 10 disclosed under 35 U.S.C. §102(b) by Simon, et al., Circulation 92(8 Suppl), 1-110 abstract 0519 (1995) in view of in view of Schwarz, et al., Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999);

(6) are claims 1-6, 8 and 10-12 disclosed under 35 U.S.C. §102(e) by U.S. Patent No. 5,976,532 in view of Schwarz, et al., Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999);

(7) are claims 1-6, 8 and 10-12 disclosed under 35 U.S.C. §102(e) by U.S. Patent No. 6,210,671 to Co, et al.;

(8) are claims 1-6, 8 and 10-12 disclosed under 35 U.S.C. §102(b) by U.S. Patent No. 4,935,234 to Todd, et al.; and

(9) are claims 1-6, 8 and 10-12 disclosed under 35 U.S.C. §103 by U.S. Patent No. 6,210,671 to Co, et al., and /or U.S. Patent No. 4,840,793 to Todd, et al., in view of Simon, et al., Circulation 92, 8 Suppl:1-110, abstract 0519 (1995); Mazzone, et al., Circulation 88:358-363 (1993); Ikeda, et al., Am. Heart J. 128:1091-1098 (1994); Inoue, et al., JACC 28:1127-1133 (1996); and Rogers, et al., Circulation 88:1215-1221 (1993).

Please note the following errors in the citations listed on page 5 and page 6 of the Examiner's Answer. On page 5 reference P) Kling *et al.* the page numbers should read "1121-1128" instead of "112-128." On page 6 reference JJ) should read "Simon *et al.*" instead of "Rogers *et al.*"

(10) The claims were also rejected on the grounds of obviousness type double patenting over U.S.S.N. 09/776,533, however this issue is mooted by the abandonment of the '533 application.

In the Examiner's Answer mailed December 9, 2004, the following rejections were withdrawn: the rejection of claim 10 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, as indefinite, and the obviousness type double patenting rejection due to the abandonment of U.S.S.N. 09/776,533.

Appellants affirm all arguments set forth in the Appeal Brief. The following remarks are submitted in response to the Examiner's Answer.

U.S.S.N.: 08/823,999
Filed: March 25, 1997
REPLY TO EXAMINER'S ANSWER

(a) Rejections under 35 U.S.C. § 112, first paragraph

(i) Claims 1-9, 11 and 12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

As reiterated by the Examiner in his Answer, the examiner's position is that the claims are drawn to "any compound" having a defined function and states that it is irrelevant that appellants' have relied upon "the disclosed limited number of known adhesion molecules or adhesion molecule-specific antibodies". However, that is exactly what appellants have done: they have relied upon the disclosure and use of **known compounds** for a new use.

The claims are not drawn to "any compound". The language of claim 1, the independent claim, reads as follows:

"administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function,

wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18,

wherein the compound is selected from the group consisting of <u>antibodies and antibody fragments</u> that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells;

molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interaction of the integrins or integrin-ligands with vascular cells or tissues,

in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue." (emphasis added)

The written description requirement was created so that one skilled in the art would know what it was that the inventors had discovered. This is abundantly clear from the claim language: a method of administering **antibodies or antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interaction of the integrins or integrin-ligands with vascular cells or tissues, wherein the integrins are Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), or CD11d/CD18.**

The integrins are fully described on pages 8-10 of the application, and were well known as of the date of the filing of this app, Antibodies to Mac-1 are described in the application at pages 9-10; a peptide fragment which blocks binding of Mac-1 is described at page 13, lines 15-19. The examples at page 22, show inhibition of binding; the examples at pages 22-23 show inhibition of restenosis in an accepted animal model. The genes encoding the integrins and their

receptors were all known and publicly available. Therefore appellants were clearly in possession of the claimed invention as of the time the application was filed.

The claims on appeal are drawn to a genus of compounds complementary to a targeted molecule and inhibiting the function of the targeted molecule. The specification describes the structure of the claimed compounds by relationship to their target, methods of preparation, and function. Regardless of the type of compound, specific binding is achieved through complementary interactions. These interactions are dependent upon hydrogen bonding. Therefore, in order for the compound to bind to the target, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location, orientation, and have the correct charge. One of skill in the art would realize that it is this arrangement that defines the structure of the compound. Complementary compounds are limited by the primary, secondary and tertiary structure of the target molecule.

In *University of Rochester*, the District Court had found claims to a method of treatment and claims to compounds for use in the method of treatment invalid as lacking enablement and written description. In *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ 1886 (Fed. Cir. 2004), the Federal Circuit reviewed the standard of the written description requirement under 35 U.S.C. 112 and reiterated that the purpose of the written description requirement is separate from the enablement requirement, and "is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventors's contribution to the field of art as described in the patent specification,' *Reiffin v. Microsoft Corp.*,

214 F.3d 1342 at 1345 (Fed. Cir. 2000). "The 'written description' requirement serves a teaching function, as a '*quid pro quo*' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time', citing to *Enzo Biochem, Inc. v. Gen-Probe Inc*, 323 F.3d 956 at 970 (Fed. Cir. 2002). *University of Rochester* at 922.

Much of the Court's discussion in *Rochester* was based on the alleged failure to disclose the structure of even a single compound as claimed. This is clearly not the case in this application. First, the claims in this case are not drawn to compounds *per se*, but to methods of use. Second, the claims are not drawn solely to the use of a class of unknown compounds defined by function alone, but to classes of compounds that are known, both by structure and by function.

The Court in *University of Rochester* did not change its previous interpretation of the requirements for compliance with the written description requirement, reiterated shortly before in *Enzo Biochem, Inc. v. Gen-Probe Inc*, 323 F.3d 956 at 970 (Fed. Cir. 2002).. The Board's attention is drawn in particular to the Court's statement in *University of Rochester* at 925, citing again to *Enzo* and stating "in fact, where there might be some basis for finding a written description requirement to be satisfied in a genetics case based on the ***complementariness*** of a nucleic acid and, for example, a protein, that correspondence might be less clear in a non-genetic situation. In *Enzo*, we explained that functional descriptions of genetic material can, in some cases, meet the written description requirement if those functional characteristics are 'coupled

with a known or disclosed correlation between function and structure, or some combination of such characteristics.' 323 F.3d at 964 (quoting from the PTO's Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106)." (emphasis added). As the Federal Circuit also stated in *University of Rochester* at 926 "We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice." The examiner's statement to the contrary, that "isolation and characterization at a minimum are required (page 8, second paragraph), is not true.

The examiner's response to appellants' argument is simple: he does not agree. He makes considerable argument and provides references beginning at page 8, but these arguments and references do not relate to written description but to enablement and are therefore discussed below.

As noted in the Appeal Brief, the claims do not stand or fall together. Independent claim 1 is discussed above. Independent claim 1 is limited to a single integrin, Mac-1 (CD11b/CD18) for which evidence has been produced using two distinct compounds, an antibody and a protein fragment. Claim 8 limits the compounds to antibodies and antibody fragments - certainly not "any compound", and indeed, well known and available for each of the named integrins at the time this application was filed. Claim 10 is limited to antibodies specifically reactive with Mac-1. This was reduced to practice as described in the examples, thereby clearly meeting the requirements under 112 for both enablement and written description.

(ii) Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled.

Appellants refer to the discussion regarding enablement in their Appeal Brief. This reviews the appropriateness of the rabbit model which appellants' used (pages 16-17; copies of the papers cited by appellants are attached in an appendix for the convenience of the Board: Coats, et al., "Remodeling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), Farb., et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-52 (1999), Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997), Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999)).

In rebuttal, the examiner has cited in the Examiner's Answer no reference other than Welt Arterioscler. Thromb. Vasc. Bio. 22:1769-1776 (2002), relying instead on argument. See page 14. It should be noted that one of the authors of Welt is an inventor of the application in issue, and that the quote by the examiner has again been taken out of context - the paper at pages 1770, col. 2 to page 1771, col. 1, and page 1772, is a review of the studies conducted by appellants which form the basis for this application, and which provides still further support for the enablement of the claimed methods.

The examiner has focused on all kinds of mere possibilities of things that can go wrong, ignoring the data in the application and which was provided subsequently and the reference provided by appellants, Topol, et al., "Long-term protection from myocardial ischemic events in

a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997), a copy of which is provided in the Appendix. He has instead again argued lack of written description for the full breadth of the compounds that can be used in the claimed method.

As reviewed in the Appeal Brief, appellants have provided both *in vitro* and *in vivo* data. This includes example 2 at page 22 of the application and Simon, et al., J. Clin. Invest. 105(3), 293-300 (February 2000), a copy of which is provided in the attached Appendix. This demonstrates efficacy in **two** animal models, a rabbit model and a mouse model.

The papers cited by the examiner do not support the rejections.

Kuntz, Science 257:1078-1031 (1992) states "Most drugs have been discovered in random screens or by exploiting information about macromolecular receptors. One source of this information is in the structures of critical proteins and nucleic acids. The structure-based approach to design couples this information with specialized computer programs to propose novel enzyme inhibitors and other therapeutic agents. Iterated design cycles have produced compounds now in clinical trials. The combination of molecular structure determination and computation is emerging as an important tool for drug development." (abstract). This supports the statements made in appellants' application, not calls them into question.

Hemker, et al., Emerging Drugs 4:175-195 (1999) seem to be irrelevant. Hemker is discussing drugs that inhibit thrombosis and noting that all of these drugs also inhibit bleeding. The claimed method does not involve the hemostatic-thrombotic system.

Pimanda, et al. Curr. Drugs Targets Cardiovas. Haematol. Disord. 3(2):101-123 (2003) states in relevant part that drugs identified through animal studies have shown benefit in treatment of restenosis. The examiner's quote is again taken out of context. Referring to page 102, the authors state immediately following the quote"Therapies in 3 broad areas have recently emerged". These are gene transfer, gene modification, and drug eluting stents. The authors reference that there is a VEGF gene transfer product doing well in clinical trials (page 102, col. 2, third paragraph); the authors discuss several ribozymes that target certain genes that produce good results in animal models (page 103, col. 1, first three paragraphs); and the authors discuss the drug eluting stents, which have proven to be highly efficacious in humans and are now FDA approved for such use. This paper therefore also supports the statements made in appellants' application.

Fattori, et al. Lancet 361:247-249 (2003) is an excellent review of the prior art compounds that have not worked to prevent restenosis, as well as the drug eluting stents that have worked quite well. Fattori also provides a long list of other promising compounds at page 247, col. 1, "Where next?" Appellants do not claim the use of any of these compounds.

There are many known and well characterized compounds that have been described in the literature that block binding to the claimed integrins. The structure and function of these

compounds are known. Appellants have demonstrated that the use of representative molecules which block the claimed integrins have been effective in preventing restenosis in an appropriate animal model. The differences between these compounds and the prior art compounds, including Topol, which the examiner has cited under the section relating to enablement, will be reviewed below.

The claims do not stand or fall together. As discussed above, claim 6 is specific to molecules inhibiting binding to Mac-1(CD11b/CD18). Claim 10 is specific to antibodies inhibiting binding to Mac-1 (CD11b/CD18) which was described in the application as filed, along with an example showing actual reduction to practice. These claims are clearly enabled. They are not drawn to "any compound" as stated by the examiner, but are limited by structure as well as function.

(b) Rejections Under 35 U.S.C. § 102 and 103

The crux of the examiner's rejection in view of the prior art is that the prior art shows a single antibody that allegedly binds to Mac-1, referred to as "c7E3", "abciximab", and "ReoPro" that has been used to treat myocardial infarction and that this method with this antibody inherently anticipates the claimed method. This antibody is actually an antibody that was made by immunization with a glycoprotein call "GPIIb/IIIa", hence the more accurate reference to the name of the antibody as an "anti-GPIIb/IIIa 7E3" (see examiner's answer on page 16). This is not an antibody that "specifically inhibits or reduces leukocyte integrin -mediated adhesion or function". The antibody has a non-specific cross-reactivity with Mac-1. Its principle reactivity

is with its intended target, GPIIb/IIIa. It does not inhibit or reduce leukocyte integrin-mediated adhesion or function.

The antibody is also not useful to prevent restenosis. It is used to diminish ischemic injury. Restenosis is an inflammatory process resulting in overproliferation of cells at the site of injury. Ischemic injury is death of cells due to a lack of oxygen. The patients are different; the dosage and schedule of treatment are different; the criteria are different; and, as amply established by the art cited by the examiner, the c7E3 antibody does not prevent restenosis.

Genetta, et al. Ann. Pharmacotherapy 30:251-257 (1996) is the principle reference relied upon by the examiner. It reports the use of the c7E3 antibody to prevent platelet aggregation during angioplasty. The examiner acknowledges there is no disclosure of treating or preventing restenosis, but argues that it would be inherent because the patients were administered the antibody during angioplasty.

As discussed repeatedly, treatment of an acute condition - myocardial infarction - is just that: a treatment over a short defined time (see col. 2, page 252 of Genetta: treatment consisted of either a single bolus or a continuous infusion over a period of 48 or 72 hours; see also col. 2, page 253, bolus or continuous infusion over 12 hours). In contrast, appellants require administration over a period of time "typically until healing has occurred, which may be as long as six months following vascular intervention, although more typically will be for four to six weeks or until acute inflammation has subsided" (page 21, last paragraph to page 22, first paragraph). The administration of the antibody, even if it met every other claim limitation

(which it does not) would not be effective in preventing restenosis because it is not administered in an effective amount - which is not only dosage but length of time of administration. To prevent restenosis, one must administer the treatment over a prolonged period of time - weeks to months.

The antibody does not have the claimed specific activity - it is active in preventing platelet aggregation, not in inhibiting or reducing leukocyte integrin mediated function. As importantly, the prior art does not described prolonged administration, which is essential for preventing or treating stenosis or restenosis..

The best evidence that this antibody does not meet the claim limitations is the ERASER study, submitted by the appellants. This paper (which is not prior art, having been published in 1999) shows that this antibody was not effective in reducing restenosis. The authors note that the mechanism of action of the antibody, which was postulated might be useful, was not inhibition of leukocyte integrin-mediated adhesion or function as claimed, but "potent platelet inhibition" (abstract). The antibody was administered as a bolus alone or in combination with one or two 12 hour infusions (a maximum of 24 hours).

Schwarz et al. Thrombosis Res. 107:121-128 (2002), Bendeck J. Vasc. Res. 38:590-599 (2001), Wu, et al. Thrombosis Res. 101:127-138 (2001) and the ERASER Investigators Circulation 100:799-806 (1999) were cited apparently in an attempt to demonstrate inherency (since a 102 rejection would normally require all elements of the claim be present in a single reference). The ERASER study is discussed above.

Wu, et al., Thrombosis Research 107:127-138 (2001) (*which is also not prior art)* does disclose the use of Abciximab in a rat model of balloon angioplasty and states that is was effective in this particular animal model (appellants' have presented evidence that the rat model is less predictive of efficacy in humans than the animal they used, but this point is not important). Wu, et al. differs from the *prior art* publications relating to the administration of this antibody not just in the animal model that is used, but also in the method of administration. One certainly has more efficacy (to the extent there is efficacy) with this antibody when it is administered over a prolonged period of time. Wu, et al. administered the antibody for periods of seven, fourteen and 28 days following injury. Wu therefore further supports the importance of the effective amount limitation in appellants' claims. This feature is also not an inherent element in Genetta.

Schwarz, et al. (*which is not prior art*) does not make up for the deficiencies in Genetta. Schwarz merely reports that abciximab inhibits the binding of various ligands to Mac-1. While this may be an inherent feature of the antibody, the paper further demonstrates that this binding activity is not selective, as required by the claims, and fails to teach the administration of an effective amount of any antibody, much less one which selectively inhibits activity, to treat or prevent stenosis or restenosis.

The Board's attention is also drawn to the articles cited by the examiner with respect to enablement (which are not relevant to enablement of the claimed subject matter since appellants' are not claiming the c7E3 antibody, but which go to the question of whether the 7E3 antibody

was used to prevent restenosis. As the art makes clear, even if the c7E3 antibody met the definition in the claims of an antibody which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function, and which blocks the interaction of the integrins or integrin-ligands with vascular cells, (which it does not), the antibody was not used to prevent restenosis but in studies relating to ischemia.

Bendeck et al. Vasc. Res. 38:590-599 (2001) is not prior art. It reports that the 7E3 antibody reduces smooth muscle cell migration. This follows a review of the studies in which the antibody (referred to in the paper as also as abciximab and ReoPro) was shown to reduce coronary events and the need for revascularization - i.e., ischemia. Not restenosis. There is no correlation between treatment for ischemia (which results in dead tissue) and restenosis or stenosis (which is due to the overproliferation of tissue). The specificity of the antibody is also reviewed at col. 2, page 590. The antibody "was developed to block glycoprotein allb/beta 3 receptors on platelets, and is used for its antithrombotic properties, and cross reacts with other recetpros on the surface of vascular smooth muscle cells and endothelial cells. Accordingly, Bendeck provides further evidence that even as of 2001, long after the priority date, the 7E3 antibody was not being used to treat or prevent restenosis or stenosis, and the antibody did not specifically inhibit or reduce leukocyte integrin-mediated adhesion or function.

In summary, the prior art relating to the use of c7E3 does not anticipate the claimed subject matter. The antibody is not specific; the antibody was used to treat acute ischemia; and the antibody was administered for only very short periods of time. In contrast, the claims require

a specific inhibitor; treatment or prevention of a chronic condition, restenosis or stenosis due to excessive tissue proliferation; and an effective amount of compound which requires long term administration.

The examiner has also relied upon Simon, et al. Circulation 92, 8 Suppl:1-110, Abstract 0519 (1995) in view of Schwarz, et al., Bendeck, et al., Wu, et al. and The ERASER Investigators, discussed above. Simon, et al. provides nothing more than Genetta, which is that the 7E3 antibody is useful to prevent or treat acute myocardial ischemia. There is no disclosure of treating patients to prevent or treat restenosis, nor of administration over a prolonged period of time.

U.S. Patent No. 5,976,532 to Coller, et al.is cumulative to Genetta and to Simon. Coller describes the treatment of acute myocardial infarction with the 7E3 antibody. The "stenosis" that the examiner refers to is an acute stenosis caused by platelet aggregation - a "clot", not stenosis resulting from a proliferation of cells at the site of injury over a period of weeks or months. This is very clear from the example at col. 29-30 that the examiner refers to - the time course is less than two days. The claims are clearly drawn to a stenosis or restenosis that is associated with a chronic condition, not an acute condition as described in Coller, et al. As the examiner admits on page 23, "Coller et al. also teach that the antibodies can be used in a variety of situations including prevent thrombosis". Appellants are not claiming a method of treating or preventing thrombosis. The only reference to dosage is found at col. 6, lines 32-47, which provides no details. The patent states repeatedly that the antibodies are useful as antithrombotic

agents and to prevent or reduce reocclusion following thrombolysis (which is not restenosis or stenosis due to proliferation of cells but blockage due to platelet aggregation). See col. 2, lines 3-6, for example.

Anderson is a general review of methods of treating or preventing restenosis as of 1993 - and does not mention any of the claimed compounds as useful or even potentially useful.

The remaining art cited by the examiner does not relate to treatment or prevention of restenosis.

Kling et al. Arterio.Kling et al. Circ. Res. 77:112-128 (1995) discloses an *in vitro* assay which demonstrates that the anti-CD18 antibody is an inhibitor of leukocyte adhesion.

There is no disclosure of administering the antibody to a patient to inhibit or reduce stenosis or restenosis as claimed; and there is no disclosure of what would constitute an effective amount. Therefore, Kling does not anticipate the claimed method.

Alteri, et al., J. Biol. Chem. 268(3):1847-1853 (1993) is similar - this paper, cited by appellants' in their application, discloses a peptide which is a claimed compound. However, the article does not disclose the claimed method because it does not disclose administering to inhibit or reduce stenosis or restenosis as claimed, nor an effective amount, as claimed.

Faxon, et al. J. Am. Coll. Cardio. 40:1199-1204 (2002) *(which is not prior art)* reports on a study to reduce infarct size in patient undergoing angioplasty for an acute myocardial infarction by administering an antibody Hu23F2G, called LeukoArrest. This antibody does inhibit the CD11/CD18 leukocyte integrin receptor. However, there is no disclosure of treating a

patient to prevent restenosis or stenosis. This would require a different treatment regime as well as dosage, since acute myocardial infarction is by definition an acute problem while restenosis and stenosis develops over a period of months.

U.S. Patent No. 6,210,671 to Co describes an antibody specifically binding to L-selectin which may be administered in combination with another antibody. The examiner references col. 18. Col. 18 lists among other antibodies an anti-Mac 1 antibody. However, no where does the reference teach administering the anti-Mac 1 antibody to prevent or treat restenosis or stenosis as claimed, much less what an effective amount would be. The examiner has made this rejection under 102(e) which requires every single claimed element to be present in the prior art reference - this standard has clearly not been met. Morever, even as to the L-selectin antibody, col. 18 makes it clear that the method is for the treatment of ischemia-reperfusion injury (see lines 30-65). This is where tissue dies from a lack of oxygen due to acute blockage; not where occlusion of a blood vessel develops over a period of weeks or months due to overproliferation of cells. These are just the opposite - one is characterized by acute blockage and cell death and the other by the development of a chronic blockage over time due to too much cell proliferation.

U.S. Patent No. 4,935,234 to Todd is the same as Co. The patent relates to the treatment or prevention of acute blockage due to myocardial infarction (see col. 6, lines 46-57), and the use of antibodies to Mac-1 to reduce inflammation by inhibiting migration of leukocytes to the injured area. Administration is very short term (col. 7, lines 9-18, 10 minute infusion). The examiner's attempt at page 27 to modify the language of the patent to make it somehow define

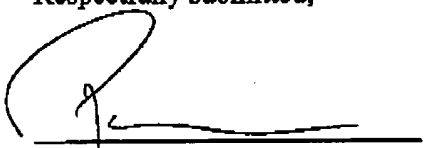
an effective amount fails because the patient class is different, the mechanism is different, and the disorder to be treated is different, from the claimed method.

The art cited above does not disclose each claimed element. The examiner has also made a rejection under 35 U.S.C. 103, arguing that these references in combination, and as further interpreted in view of references that refer to the various claimed compounds (the ones the examiner says are not enabled), would make obvious the claimed method. First, none of the art teaches that one must have a compound as claim, second to treat or prevent restenosis or stenosis resulting from the specific conditions named, in an effective amount. Therefore the art cannot make obvious this combination since the elements are simply not present in the art. No where does the art recognize that the treatment must be over a prolonged period of time to be an effective dosage. No where does the art teach that one should use compounds having known activity in preventing platelet aggregation and other thrombotic events and use them for a completely different indication having a different mechanism of action resulting not in cell death due to ischemia but over proliferation of cells (as in restenosis and stenosis as claimed). The law under 35 U.S.C. 103 is clear: you must have art showing the claimed elements, the motivation to combine, and a reasonable expectation of success. Even with hindsight, the art does not provide each of the claimed elements, much less the motivation to combine, and even less so the reasonable expectation of success. Accordingly, the claims are not obvious over the cited art, alone or in combination or interpreted in view of post filing art.

U.S.S.N.: 08/823,999
Filed: March 25, 1997
REPLY TO EXAMINER'S ANSWER

For the foregoing reasons, Appellant submits that claims 1-12 are definite, comply with the written description requirement, are enabled, novel and non-obvious.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: February 9, 2005

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)